REMARKS

Upon entry of the instant amendment, claims 1 and 7-15 will remain pending in the above-identified application and stand ready for further action on the merits.

In this Amendment, claims 1 and 15 have been amended, and claims 2-6 have been canceled.

Support for amended claims 1 and 15 can be found in paragraphs [0026], [0027] and Examples 1 to 6 of the present specification. For example, it is noted that the phrase "toluene, in which appropriate quantities of soluble solvent is added," that now occurs in amended claims 1 and 15 is supported at least by the description "a mixed solvent (560ml of toluene: 140ml of methanol)" as described in Examples 2 and 6 of the present specification.

Accordingly, the present amendments to the claims do not introduce new matter into the application as originally filed. As such entry of the instant amendment and favorable action on the merits is earnestly solicited at present.

Claims Rejections under 35 U.S.C. § 103(a)

Claims 1-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **JP 1-79151** or **JP 4-187674** in view of **JP 64-79151** supplemented with **US 4,895,841** and **JP 4-187674** supplemented with **CA 118:124398 (1992)**.

Reconsideration and withdraw of the instant rejection of the claims is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

MPEP § 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

(a) determining the scope and content of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP § 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Exemplary rationales that may support a conclusion of obviousness include:

(a) combining prior art elements according to known methods to yield predictable results;

(b) simple substitution of one known element for another to obtain predictable results;

(c) use of known technique to improve similar devices (methods, or products) in the same way;

(d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(e) "obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success

(f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03.

Distinctions Over the Cited Art

As Regards Raney Nickel Catalyst —

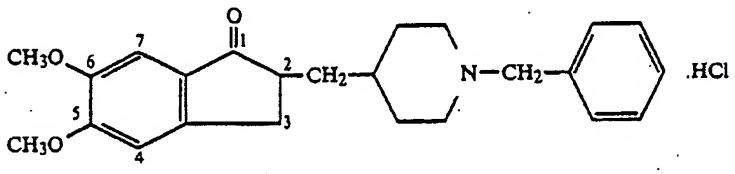
JP1-79151A or **JP2578475B** (*hereinafter referred to as **D1***) discloses a compound having acetylcholinesterase inhibiting property as represented by donepezil hydrochloride and a preparation thereof, and it shows "examples" of a catalyst to be used in catalytic reduction of (C) to (D), *shown at below page 10*, such as Pd-C (see Example 4) and Raney nickel (Ra-Ni), but there is no specific disclosure about the catalytic reduction process using Ra-Ni as the catalyst.

JP2578475B (*hereinafter referred to as **D2***) is a patent on a divisional application from the application of D1 and describes Production Example 1 that uses Pd-C. D2 describes the example using Pd-C but does not describe the example using Ra-Ni.

Please note that Example 4 of D1 is same as Production Example 1 of D2, and they correspond to Example 4 at column 34 of **US 4,895,841** (*shown below*).

EXAMPLE 4

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]-methyl-piperidine hydrochloride



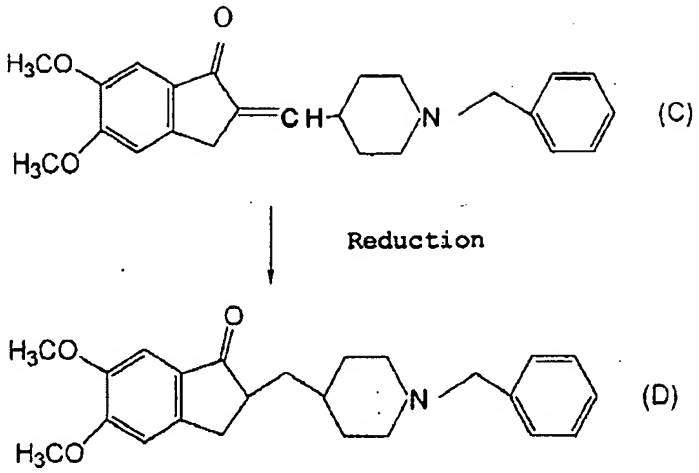
0.4 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine was dissolved in 16 ml of THF, followed by addition of 0.04 g of 10% palladium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 6 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride: methanol=50:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.36 g (yield: 82%) of the title compound having the following properties:

m.p. (°C.): 211°-212° C. (dec.) elementary analysis: $C_{24}H_{29}NO_3.HCl$

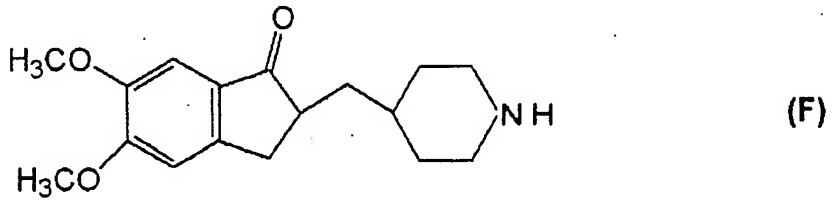
	C	H	N
calculated (%)	69.30	7.27	3.37
found (%)	69.33	7.15	3.22

JP4-187674A (*hereinafter referred to as **D3***) discloses a process for preparing an optically active compound of "donepezil", which is described in D1 and D2, by using an asymmetric reduction catalyst, *i.e.* an expensive ruthenium-BINAP complex catalyst.

Namely, D1 to D3 all disclose the following reaction formula as shown below.



In the process of D1 to D3, a compound of the structural formula (F) at page 7 of the present specification, *i.e.*, a debenzylated compound, as an impurity is excessively produced, and thus column purification is needed.



However, said column purification takes time and costs so much, there is a need for a development of the process for industrially, economically and easily preparing the compound of structural formula II in claim 1 of the present specification. The present inventors have found that the production of said debenzylated compound is unexpectedly curtailed by using the Ra-Ni catalyst. Since the Ra-Ni catalyst is likely to ignite spontaneously because of its hydrogen adsorption when it becomes dry, it has been considered that Ra-Ni is not suitable for a large-

scale industrial production. The present inventors have completed the efficient process for the compound of formula II and salts thereof, which is characterized by a selective reductive reaction of olefins using the Ra-Ni catalyst. Donepezil hydrochloride is now prepared industrially by the process of the present invention.

In addition, according to Example 1 of D3, it describes that "Methylene chloride was removed under reduced pressure(20mmHg), and 0.1N 180ml hydrochloric acid was added into a residue to obtain a hydrochloride (pH=2). A catalyst was extracted twice by ethyl acetate 50ml and a sodium carbonate solution was added to an aqueous layer to adjust pH 9. The aqueous layer was extracted twice by methylene chloride 30ml".

Accordingly, the process of D3 requires a cumbersome separating operation because the ruthenium-RINAP complex catalyst is the homogenous catalyst. On the other hand, the process of the present invention is easy to operate, which is an advantageous effect of the present invention over D3.

As Regards Purity —

The USPTO alleges that there are no statistics as to a comparison of whether the purity is "statistically significant" over the purity of the prior art.

Table 1 at page 18 of the present specification (*see below*) shows the comparison of the purity in hydrogenated reaction solution between the present invention (Example 1 to 9) and the prior art (Reference Examples 1 to 3).

Table 1 (Page 18 of the instant specification)

Test Sample	Hydrogenated reaction solution, Purity (%)	Purity of donepezil hydrochloride or donepezil* (%)
Example 1	99.6	99.8
Example 2	99.0	99.8
Example 3	99.1	99.7
Example 4	99.4	99.8
Example 5	99.1	99.8
Example 6	99.0	99.4
Example 7	96.5	99.0*
Example 8	95.8	98.8*
Example 9	97.8	99.6*
Reference Example 1	85.8	N.T.
Reference Example 2	91.5	N.T.
Reference Example 3	75.2	N.T.

Moreover, pages 7 to 8 of the **ICH guideline** titled as "**Impurities in new drug substances**", *attached hereto*, describes that, if reporting threshold, which is a limit above which an impurity should be reported, is 0.05% (maximum daily dose is ≤2g/day) or 0.03% (maximum daily dose is >2g/day), the biological safety of the impurity should be qualified. In view of this description of the ICH guideline, the difference of the purity between Examples 1 to 9 and Reference Examples 1 to 3 as shown in Table 1 is significant. Therefore, the selectivity of the Ra-Ni catalyst is evidently high.

Furthermore, according to Examples of D3, the chemical purity of the compound prepared by the process of D3 is as follows.

Example 1	91.3%
Example 2	98%
Example 3	95.7%

On the other hand, Table 1 at page 18 of the present specification shows the purity of the compound prepared by the process of the present invention is from 98.8% to 99.8%. In view of the above-mentioned ICH guideline, it is submitted that the purity described in **Table 1** of the present specification is significantly and evidently higher than the purity of D3.

The USPTO also alleges that in the prior art process, after production of the desired formula II, the product was dried and the residue was obtained, while in the instant process, after production of the desired formula II (Examples 1-5, 7-9), "subsequently" the product was crystallized from ethanol.

However, the above opinion of the USPTO is improper, because in the process of D1 and D2, the residue was purified by making use of a silica gel column chromatography (see Example 4 of US 4,895,841). Furthermore, please note that in the instant process, after production of the desired formula II, the solution "was crystallized", in other words, "was isolated". In this context, "crystallization" in the instant process is not for purification, but for isolation.

Accordingly, the instant process does not require the process of purification because the selectivity of the Ra-Ni catalyst is high and thus the purity of hydrogenated reaction is sufficiently high.

Moreover, in Example 6 of the present specification, crystallization, *i.e.* isolation after the reductive reaction was not conducted. Thus Example 6 shows that, in the instant process, donepezil hydrochloride with the high purity can be prepared without not only column chromatography but also isolation by crystallization.

The following **Table A** data shows a comparison of the impurity, although the same is not described in the present specification as originally filed.

Table A

Test Sample of the present specification	Hydrogenated reaction solution, Purity (%)	Impurity (%)	
		Debenzylated compound	Raw material
Example 1	99.6	0.15	ND
Example 2	99.0	0.34	ND
Example 3	99.1	0.25	0.23
Example 4	99.4	0.23	ND
Example 5	99.1	0.07	ND
Example 6	99.0	0.31	ND
Example 7	96.5	2.83	ND
Example 8	95.8	2.80	0.54
Example 9	97.8	1.36	0.31
Reference Example 1	85.8	13.4	ND
Reference Example 2	91.5	5.74	1.30
Reference Example 3	75.2	23.2	ND

As Regards Motivation —

The USPTO alleges that one having ordinary skill in the art in possession of the above references D1 to D3 would be motivated to employ any generically taught hydrogenation catalyst for the particular process because the prior art has explicitly demonstrated the variation of operable catalysts and generically provided optional variations for the exemplified species.

However, as mentioned above, since the Ra-Ni catalyst is likely to ignite spontaneously because of its hydrogen adsorption when it becomes dry, it has been considered that Ra-Ni is not suitable for the large-scale industrial production. Ra-Ni soaked in water is available and the water is generally replaced with a solvent when it is used. However, the flammable solvent such as THF has been considered not to be suitable for the replacement.

In fact, not only above mentioned D1 to D3 but also patent publications and references published by other companies (*listed below*) do not disclose the specific example using the Ra-Ni catalyst. It is submitted that this fact demonstrates that there would have been no motivation to employ the Ra-Ni catalyst for one of ordinary skill in the art.

<Patent publications and references published by other companies>

- W02008/010235→NaBH4/CoC12
- WO2007/119118 → Pt-C
- WO2007/108011 → Pt-C
- US2007/0191610 → Pd-C
- WO2007/077443 → Pd-C
- New Synthesis of Donepezil Through Palladium-Catalyzed Hydrogenation Approach; SYNTHETIC COMMUNICATIONS, 36:169-174 (2006)
- Efficient and Industrially Viable Synthesis of Donepezil; SYNTHETIC COMMUNICATIONS, 37:2847-2853 (2007)
- An Improved and Efficient Process for the Production of Donepezil Hydrochloride: Substitution of Sodium Hydroxide for n-Butyl Lithium via Phase Transfer Catalysis; ORGANIC PROCESS RESEARCH & DEVELOPMENT, 12(4), pp731-735 (2008).

Furthermore, as shown in the above **Table A**, when solvents having a high solubility for raw materials such as methanol were used, the production of debenzylated compound was not fully suppressed (see Example 7 to 9). On the other hand, when solvents having a low solubility for raw materials such as THF and toluene, which are both flammable, the production of said debenzylated compound was fully curtailed.

The currently amended claims 1 and 15 require the condition that the raw materials are reacted in the solvent of THF or toluene, both of which have the low solubility for raw materials and are flammable. Therefore, it would have never been thought of by one of ordinary skill in the art to choose the Ra-Ni catalyst, which is likely to ignite spontaneously, in combination with THF or toluene as instant invention. Moreover, it is submitted that the advantageous effect that the production of said debenzylated compound can be fully curtailed by the combination of the Ra-Ni catalyst and the reaction solvent such as THF or toluene cannot be expected from the cited references.

CONCLUSION

Based upon the amendments and remarks presented herein, the USPTO is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1 and 7-15 are allowable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey, Reg. No. 32,881 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: June 24, 2009

Respectfully submitted,

By _____

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Attachment: ICH guideline titled as "**Impurities in new drug substances**" (14 pages)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES IN NEW DRUG SUBSTANCES
Q3A(R2)

Current *Step 4* version

dated 25 October 2006

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q3A(R2)
Document History

First Codification	History	Date	New Codification November 2005
Q3	Approval by the Steering Committee under *Step 2* and release for public consultation.	15 March 1994	Q3A
Q3A	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. Q3 was renamed Q3A.	30 March 1995	Q3A
Q3A(R)	Approval by the Steering Committee of the first Revision under *Step 2* and release for public consultation.	7 October 1999	Q3A(R1)
Q3A(R)	Approval by the Steering Committee of the first Revision under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	6 February 2002	Q3A(R1)

Current *Step 4* version

Q3A(R2)	Approval by the Steering Committee of the revision of the Attachment 2 directly under *Step 4* without further public consultation.	25 October 2006	Q3A(R2)

IMPURITIES IN NEW DRUG SUBSTANCES

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 7 February 2002, this guideline is recommended for adoption to the three regulatory parties to ICH.

Attachment 2 has been revised on 25 October 2006.

TABLE OF CONTENTS

IMPURITIES IN NEW DRUG SUBSTANCES

1. PREAMBLE

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from two perspectives:

Chemistry Aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and

Safety Aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

2. CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are

generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as Good Manufacturing Practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

3. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

3.1 Organic Impurities

The applicant should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarise the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH Guideline Q1A on Stability) used to identify potential impurities arising during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences discussed.

The studies conducted to characterise the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described. Note that any impurity at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than (≤) the identification thresholds, it is useful also to report the results of these studies.

Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold. All impurities should be qualified as described later in this guideline.

3.2 Inorganic Impurities

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed.

Acceptance criteria should be based on pharmacopoeial standards or known safety data.

3.3 Solvents

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C Guideline for Residual Solvents.

4. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B Guidelines for Analytical Validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds (See Attachment 1) does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be acceptable where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterised according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

5. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as "complies", "meets limit" etc. Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time. If a higher reporting threshold is proposed, it should

be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.

For each batch of the new drug substance, the report should include:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedure used

6. LISTING OF IMPURITIES IN SPECIFICATIONS

The specification for a new drug substance should include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities in the new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities" in this guideline. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in the specification should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Specified, unidentified impurities should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A", "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by safety data, and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of the new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A Guideline on Specifications, Decision Tree #1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds (See Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified impurities and total impurities.

In summary, the new drug substance specification should include, where applicable, the following list of impurities:

Organic Impurities

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Residual Solvents

Inorganic Impurities

7. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in Attachment 1 are exceeded.

Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient

population, drug class effects, clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification" (Attachment 3) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process. Any new impurity observed in later stages of development should be identified if its level is greater than (>) the identification threshold given in Attachment 1 (see the "Decision Tree for Identification and Qualification" in Attachment 3). Similarly, the qualification of the impurity should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.

8. GLOSSARY

Chemical Development Studies: Studies conducted to scale-up, optimise, and validate the manufacturing process for a new drug substance.

Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image.

Extraneous Contaminant: An impurity arising from any source extraneous to the manufacturing process.

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present.

Identified Impurity: An impurity for which a structural characterisation has been achieved.

Identification Threshold: A limit above (>) which an impurity should be identified.

Impurity: Any component of the new drug substance that is not the chemical entity defined as the new drug substance.

Impurity Profile: A description of the identified and unidentified impurities present in a new drug substance.

Intermediate: A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance.

Ligand: An agent with a strong affinity to a metal ion.

New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphic Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms.

Potential Impurity: An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification Threshold: A limit above (>) which an impurity should be qualified.

Reagent: A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a new drug substance.

Reporting Threshold: A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

Starting Material: A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Unidentified Impurity: An impurity for which a structural characterisation has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification.

ATTACHMENT 1
Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[1] The amount of drug substance administered per day

[2] Higher reporting thresholds should be scientifically justified

[3] Lower thresholds can be appropriate if the impurity is unusually toxic

ATTACHMENT 2

Illustration of Reporting Impurity Results for Identification and Qualification in an Application

The attachment is only illustrative and is not intended to serve as template how results on impurities should be presented in an application file. Normally raw data are not presented.

Example 1: 0.5 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[1)]	0.6	Yes	None[1)]
0.1649	0.16[1)]	0.8	Yes	Yes[1)]

Example 2: 0.8 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

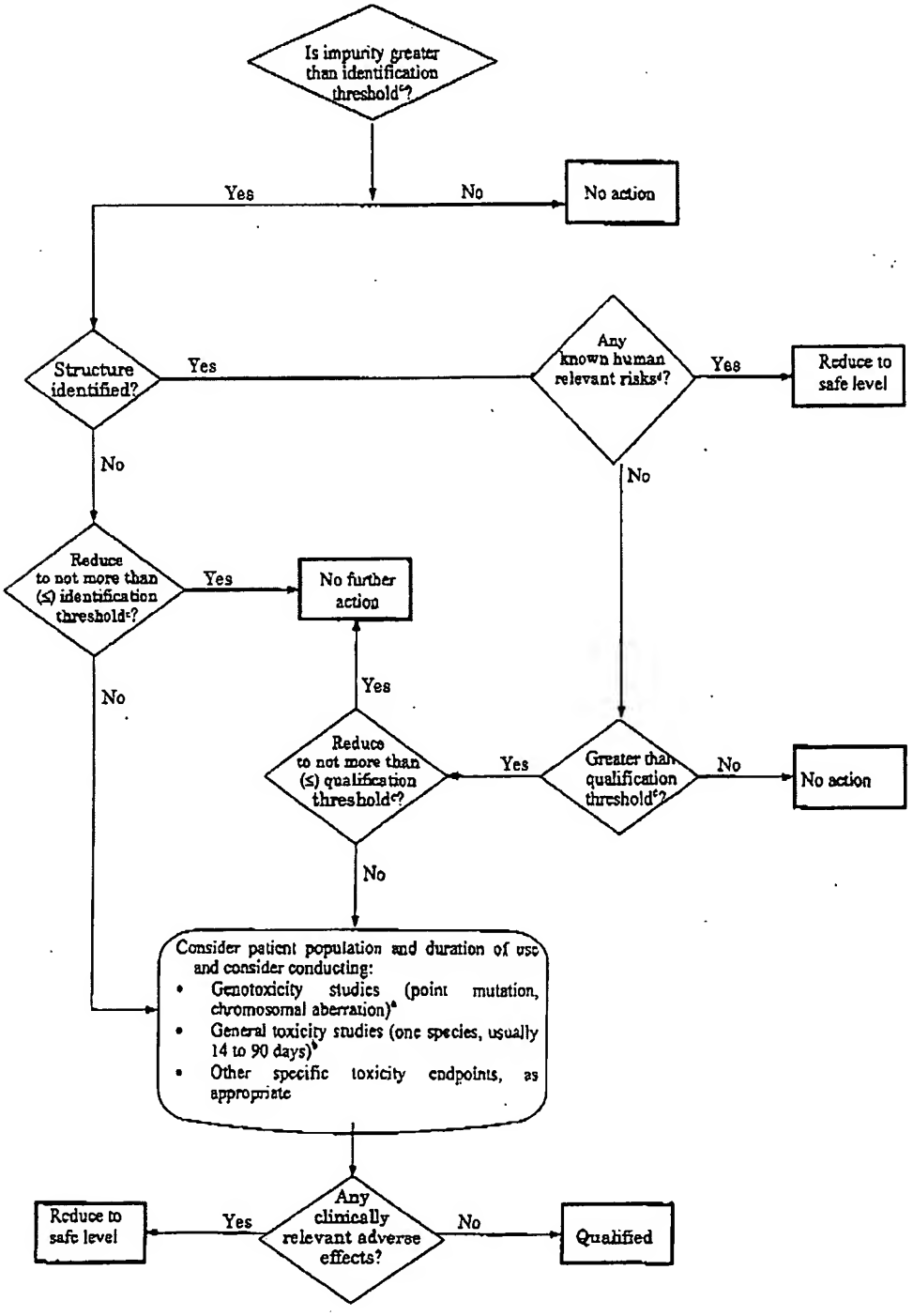
"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	yes	None[1)2)]
0.143	0.14	1.1	yes	Yes[1)]

1) After identification, if the response factor is determined to differ significantly from the original assumptions, it may be appropriate to re-measure the actual amount of the impurity present and re-evaluate against the qualification threshold (see Attachment 1).

2) To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: when the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold and compared to the threshold. For example the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount) which is then rounded up to 1.0 mg; so the qualification threshold expressed in TDI (1.0 mg) is not exceeded.

ATTACHMENT 3

Decision Tree for Identification and Qualification



Notes on Attachment 3

a) If considered desirable, a minimum screen (e.g., genotoxic potential), should be conducted.
A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

b) If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

c) Lower thresholds can be appropriate if the impurity is unusually toxic.

d) For example, do known safety data for this impurity or its structural class preclude human exposure at the concentration present?